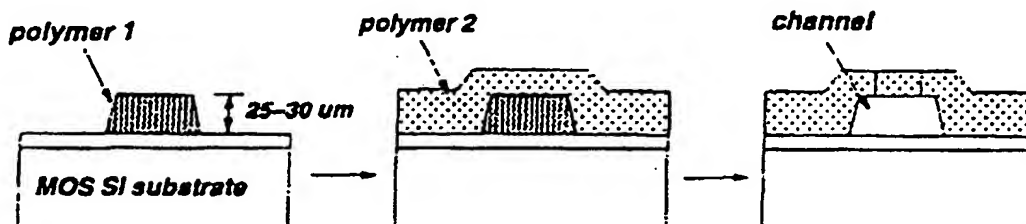




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| (51) International Patent Classification ⁶ : G03F 7/00 | | A1 | (11) International Publication Number: WO 98/07069 |
| | | | (43) International Publication Date: 19 February 1998 (19.02.98) |
| (21) International Application Number: PCT/US97/14054 | | (74) Agents: CARROLL, Peter, G. et al.; Medlen & Carroll, LLP, Suite 2200, 220 Montgomery Street, San Francisco, CA 94104 (US). | |
| (22) International Filing Date: 11 August 1997 (11.08.97) | | | |
| (30) Priority Data: 60/023,393 12 August 1996 (12.08.96) US 08/807,184 6 August 1997 (06.08.97) US | | (81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). | |
| (60) Parent Application or Grant (63) Related by Continuation US Not furnished (CIP) Filed on Not furnished | | Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> | |
| (71) Applicant (for all designated States except US): THE REGENTS OF THE UNIVERSITY OF MICHIGAN [US/US]; Wolverine Tower, Room 2071, 3003 South State Street, Ann Arbor, MI 48109-1280 (US). | | | |
| (72) Inventors; and | | | |
| (75) Inventors/Applicants (for US only): MASTRANGELO, Carlos, H. [US/US]; 5844 Creekview Court, Ann Arbor, MI 48105 (US). MAN, Piu, F. [CA/US]; Suite 109, 536 S. Forest Avenue, Ann Arbor, MI 48104 (US). WEBSTER, James, R. [US/US]; 9319 Harbor Cove Circle #312, Whitmore Lake, MI 48189 (US). | | | |

(54) Title: POLYMER-BASED MICROMACHINING TECHNOLOGY FOR MICROFLUIDIC DEVICES



Simplified fabrication process for plastic channels.

(57) Abstract

The present invention relates to polymer-based micro-electro-mechanical system (MEMS) technology suitable for the fabrication of integrated microfluidic systems, particularly medical and chemical diagnostics system, ink-jet printer head, as well as any devices that requires liquid- or gas-filled cavities for operation. The integrated microfluidic systems may consist of pumps, valves, channels, reservoirs cavities, reaction chambers, mixers, heaters, fluidic interconnects, diffusers, nozzles, and other microfluidic components on top of a regular circuit substrate. This technology is vastly superior than any alternatives available such as glass-based, polysilicon-based MEMS technology as well as hybrid "circuit board" technology because of its simple construction low cost, low temperature processing, and its ability to integrate any electronic circuitry easily along with the fluidic parts.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|------------------------------------------|----|----------------------------------------------|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | | Republic of Korea | PT | Portugal | | |
| CN | China | KR | Republic of Korea | RO | Romania | | |
| CU | Cuba | KZ | Kazakhstan | RU | Russian Federation | | |
| CZ | Czech Republic | LC | Saint Lucia | SD | Sudan | | |
| DE | Germany | LI | Liechtenstein | SE | Sweden | | |
| DK | Denmark | LK | Sri Lanka | SG | Singapore | | |
| EE | Estonia | LR | Liberia | | | | |

POLYMER-BASED MICROMACHINING TECHNOLOGY FOR MICROFLUIDIC DEVICES

This invention was made with U.S. government support under grant NIH-R01-
5 H601044 awarded by the National Institutes of Health. The U.S. government has certain
rights in the invention.

FIELD OF THE INVENTION

The present invention relates to compounds and methods for micromachining, and in
10 particular, polymer-based technology for fabricating microfluidic devices.

BACKGROUND

Microfluidic systems are highly useful in medical diagnostics, environmental
monitorings, biological food testing, chemical sensing and analysis. Current efforts on the
15 fabrication of microfluidic systems and fluidic technologies have been mainly focused on
individual component development. Individual components such as pumps [See M. Esashi *et al.* "Normally Close Microvalve and Micropump Fabricated on a Silicon Wafer," in
International Workshop on Micro Electromechanical Systems (MEMS 89), pp. 29-34 (1989);
R. Zengerie *et al.* "A Micro Membrane Pump with Electrostatic Actuation," in *International*
20 *Workshop on Micro Electromechanical Systems (MEMS 92)*, pp. 19-24 (1992); W. Zang and
C.H. Ahn, "A Bi-directional Magnetic Micropump on a Silicon Wafer," in *International*
Workshop on Solid-State Sensors and Actuators (Hilton Head '96), pp. 94-97 (1996)], valves
[See T. Ohnstein *et al.* "Micromachined Silicon Valve," in *International Workshop on Solid-*
State Sensors and Actuators (Hilton Head '90), pp.95-97 (1990); J.G. Smith, "Piezoelectric
25 Micropump with Three Valves Working Peristaltically," *Sensors and Actuators*, Vol. A21-23,
pp. 203-206 (1990); Y.-C Lin *et al.* "Characteristics of a Polyamide Microvalve," in
International Workshop on Solid-State Sensors and Actuators (Hilton Head '96), pp. 113-116
(1996)], fluidic channels [J. Pfahler *et al.* "Liquid Transport in Micron and Submicron
Channels," *Sensors and Actuators*, Vol. A21-23, pp. 431-434 (1990)], reaction chambers [S.
30 Nakagawa *et al.* "A Micro Chemical Analyzing System Integrated on a Silicon Wafer," in
International Workshop on Solid-State Sensors and Actuators (Hilton Head '90), pp. 89-94
(1990)], separation stages [D.J. Harrison *et al.* "Chemical Analysis and Electrophoresis

Systems Integrated on Glass and Silicon Chips," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '92)*, pp. 110-113 (1992); A. Manz *et al.*, "Integrated Electroosmotic Pumps and Flow Manifolds for Total Chemical Analysis Systems," in *Transducers '91*, pp. 939-941 (1991); A. Manz *et al.*, "Planar Chips Technology for Miniaturization and Integration of Separation Techniques into Monitoring Systems: Capillary Electrophoresis on a Chip," *J. Chromatography*, Vol. 593, pp. 253-258 (1992)] and detection techniques [R.C. Anderson, G.J. Bodgdan and R.J. Lipshutz, "Miniaturized Genetic Analysis System," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 258-261 (1996)], have been fabricated using a sundry of technologies. Numerous fluidic propulsional methods have also been developed based on mechanical pumping, pneumatic forces, electrosmosis [D.J. Harrison *et al.*, "Miniaturized Chemical Analysis Systems Based on Electrophoretic Separations and Electroosmotic Pumping," in *Transducers '93*, pp. 403-406 (1993)], dielectrophoresis [H.A. Pohl, *Dielectrophoresis*, Cambridge: Cambridge University Press (1978)], surface tension gradients [M.A. Burns *et al.*, "Microfabricated Structures for Integrated DNA Analysis," *Proc. Natl. Acad. Sci. USA*, 93:5556-5561 (1996); H. Matsumoto and J.E. Colgate, "Preliminary Investigation of Micropumping Based on Electrical Control of Interfacial Tension," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '90)*, pp. 105-110 (1990); G. Beni and M.A. Tenan, "Dynamics of Electrowetting Displays," *J. Appl. Phys.*, Vol. 52, pp. 6011-6015 (1981), bubble generation [L. Lin *et al.*, "Microbubble Powered Actuator," in *Transducers '91*, pp. 1041-1044 (1991)], and evaporation-condensation [T.K. Jun and C.J. Kim, "Microscale Pumping with Traversing Bubbles in Microchannels," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 144-147 (1996)].

However, efforts on system integration of components to date have been limited [S.C. Terry *et al.*, "A Gas Chromatographic Air Analyzer Fabricated on a Silicon Wafer," *IEEE Trans. on Electron Devices*, Vol. ED-26, pp. 1880-1886 (1979); A. van der Berg and P. Bergveld, *Micro Total Analysis Systems*, New York: Kluwer (1994)], which mainly include the use of bulk micromachining and surface micromachining technology. Both of them lack simple construction of components and the capability to integrate all of components with electronic circuitry.

Bulk micromachining technology, which includes the use of glass wafer processing, silicon-to-glass wafer bonding, has been commonly used to fabricate individual microfluidic components. In Europe, this glass-bonding technology has also been used to fabricate

microfluidic systems. In these systems, the control electronics are implemented on a hybrid manner external to the system. This system integration method has several problems.

Because these systems rely on bonding of substrates, it is essential that the bonding surfaces create an hermetic seal to prevent the leakage of chemicals and reagents. This poses a great difficulty when interconnection leads are present on the bonding surfaces which prevent the surfaces from being flat. It is well known that it is exceedingly difficult to attain good bonds even using well-characterized techniques such as anodic bonding when steps on the bonding surfaces exceed 0.2 μm . Because of this planarity requirement, these devices require either complex planarization schemes, or the use of diffused leads. Because of these difficulties, only relatively simple fluidic systems can be constructed using this scheme.

Unlike bulk micromachining, surface micromachining technology can be used to fabricate individual fluidic components as well as microfluidic systems with on-chip electronics. In addition, unlike bonded-type devices, hermetic channels can be built in a relatively simple manner using channel walls made of polysilicon [J.R. Webster *et al.*, "Monolithic Capillary Gel Electrophoresis Stage with On-Chip Detector," in *International Conference on Micro Electromechanical Systems (MEMS 96)*, pp. 491-496 (1996)], silicon nitride [C.H. Mastrangelo and R.S. Mullet, "Vacuum-Sealed Silicon Micromachined Incandescent Light Source," in *Int. Electron Devices Meeting (IDEM 89)*, pp. 503-506 (1989)] and silicon dioxide. Surface micromachined channels that are constructed with these thin films have two basic problems. Because the thickness of the films is limited to a few microns, the height of cavities and channels is very small ($< 5 \mu\text{m}$) resulting in sub-pL sample volumes. These exceedingly small sample volumes both strain the requirements for the sensitivity limits of detection schemes and also aggravate the surface adsorption of samples and reagents on the wall which further diminishes the sample concentration. On the fabrication side, due to the strong nature of the silicon based building materials, the formation of long capillaries is difficult to accomplish. This is because the etchants used for the sacrificial etch are relatively slow and in many cases extremely reactive (such as hydrofluoric acid HF). In these structures, it is customary to leave devices in the sacrificial etch solution for many hours. Special passivation layers (primarily silicon nitride SiN) are used to passivate any active electronic devices that must survive the sacrificial etch.

What is needed is micromachining technology that allows for fabrication of channels with a flexibility in cross section and channel length at virtually no loss in system performance. In addition, the technology should be low cost and should not require specialized equipment.

5

SUMMARY OF THE INVENTION

The present invention relates to polymer-based micro-electro-mechanical system (MEMS) technology suitable for the fabrication of integrated microfluidic systems, particularly medical and chemical diagnostics system, ink-jet printer head, as well as any devices that requires liquid- or gas-filled cavities for operation. The integrated microfluidic systems may consist of pumps, valves, channels, reservoirs, cavities, reaction chambers, mixers, heaters, fluidic interconnects, diffusers, nozzles, and other microfluidic components on top of a regular circuit substrate. This technology is vastly superior than any alternatives available such as glass-based, polysilicon-based, MEMS technology as well as hybrid 'circuit board' technology (See e.g. D. VerLee *et al.*, "Fluid Circuit Technology: Integrated Interconnect Technology for Miniature Fluidic Devices," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 9-12 (1996); R.C. Anderson *et al.*, "Miniaturized Genetic Analysis System," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 258-261 (1996); M. Albin *et al.*, "Micromachining and Microgenetics: Where Are They and Where Do They Work Together," in *International Workshop on Solid-State Sensors and Actuators (Hilton Head '96)*, pp. 253-257 (1996), where plastic have been used because of its high versatility to provide transparent surfaces and benign surfaces].

The present invention contemplates both methods and devices. In one embodiment, the present invention contemplates a method for fabricating microchannels, comprising the steps: a) providing a substrate, said substrate having upper and lower surfaces; b) depositing a first polymer layer on said upper surface of said substrate, said first polymer layer having i) a lower surface contacting said upper surface of said substrate and ii) an upper surface; c) depositing a second polymer layer on said upper surface of said first polymer layer, said second polymer layer having i) a lower surface contacting said upper surface of said first polymer layer and ii) an upper surface; and d) sacrificially etching said first polymer layer under conditions such that said second polymer layer comprises walls of a microchannel.

In another embodiment, the present invention contemplates a method for fabricating microchannels, comprising the steps: a) providing a silicon substrate, said silicon substrate having upper and lower surfaces; b) depositing a first polymer layer on said upper surface of said silicon substrate, said first polymer layer having i) a lower surface contacting said upper surface of said silicon substrate and ii) an upper surface; c) photolithographically defining said first polymer layer under conditions such that said first polymer layer has a desired thickness; d) depositing a second polymer layer on said upper surface of said first polymer layer, said second polymer layer having i) a lower surface contacting said upper surface of said first polymer layer and ii) an upper surface; and e) sacrificially etching said first polymer layer under conditions such that said second polymer layer comprises walls of a microchannel.

It is not intended that the microchannels of the present invention be limited to any specific dimensions. In one embodiment, the desired thickness of said first polymer layer is between 0.5 and 200 μ and this thickness defines the height of the channel.

Of course, the present invention contemplates additional fabrication steps. In one embodiment, the present invention contemplates, prior to step (d) the step of photolithographically defining said second polymer layer. In another embodiment, the present invention contemplates after step (d) the step (e) of etching openings in said walls of said microchannel. In yet another embodiment, the present invention contemplates after step (d) and before step (e) the step of depositing a third polymer layer on said upper surface of said second polymer layer.

It is not intended that the present invention be limited by the particular type of polymers. Polymers include, but are not limited to, photoresist, polyamide, benzocyclobutene, polydimethylsiloxane, vapor-deposited p-xylylene, pTFE, PMMA, p-HMDS, polypropylene, starch-based polymers, epoxy, and acrylics. In one embodiment, polymer pairs are selected wherein the first polymer is soluble in a particular solvent, while the second polymer is not soluble in the same solvent. This permits the use of the polymer pair such that sacrificial etching with the solvent (or a mixture of solvents) removes the first polymer but leaves the second polymer intact to serve as the polymer for the microchannel.

It is not intended that the present invention be limited by the particular barrier layer if used. The barrier layers include, but is not limited to, metal, stack of different metals, polymers, silicon-based materials, and other inorganic materials.

The present invention contemplates numerous arrangements of the various polymer layers. For example, in one embodiment, the present invention contemplates a method for

fabricating microchannels, comprising the steps: a) providing a silicon wafer, said silicon wafer having upper and lower surfaces; b) depositing a first layer of a first polymer on said upper surface of said silicon wafer, said first polymer layer having i) a lower surface contacting said upper surface of said silicon wafer and ii) an upper surface; c) depositing a second polymer layer on said upper surface of said first layer, said second polymer layer having i) a lower surface contacting said upper surface of said first layer and ii) an upper surface; d) photolithographically defining said second polymer layer under conditions such that said second polymer layer has a thickness between 0.5 and 200 μ ; e) depositing a second layer of said first polymer on said upper surface of said second polymer layer, said second layer of said first polymer having i) a lower surface contacting said upper surface of said second polymer layer and ii) an upper surface; f) sacrificially etching said second polymer layer under conditions such that said first and second layers of said first polymer comprise walls of a microchannel, said microchannel having a height defined by said thickness of said second polymer layer of step (d); and g) etching one or more openings in said walls of said microchannel.

This latter embodiment can also contain additional polymers. In one embodiment, the method further comprises after step (e) and before step (f) the step of depositing a layer of a third polymer on said upper surface of said second layer of said first polymer.

Again, the present invention is not limited to particular polymers. In the latter embodiment of the method of the present invention, it is preferred that said first and second layers of said first polymer comprise vapor-deposited p-xylylene.

The present invention is not limited to the nature of number of openings. In one embodiment, first and second openings are etched, said first opening serving as an inlet and said second opening serving as an outlet. In one embodiment, said openings are etched from said lower surface of said silicon wafer into said lower surface of said first layer of said first polymer. In another embodiment, said openings are etched from said upper surface of said layer of said third polymer into said upper surface of said second layer of said first polymer.

The polymer-based micromachining technology proposed here encompasses the combined benefits of the plastic fluidic technologies while capable of integration of active microfluidic and electronic devices on a monolithic package. Hermetically sealed channels can be fabricated with a flexibility in cross section and channel length at virtually no loss in system performance. System integration is realized by the ability to fabricate various fluidic components using the same process on top of standard yet complex MOS control circuitry. In

addition, the polymer technology of the present invention is very low cost and does not require specialized equipment.

The devices of the present invention, once fabricated, have a variety of uses. In one embodiment, the present invention contemplates a polymer microchannel fabricated on a silicon substrate, wherein said polymer microchannel is capable of conveying liquids or gases (or both). The present invention is not limited by the nature of the liquid or gas. In one embodiment, the present invention contemplates a polymer microchannel fabricated on a silicon substrate, said microchannel containing one or more microdroplets. In another embodiment, the present invention contemplates a polymer microchannel fabricated on a silicon substrate, said microchannel connected to a reaction chamber, said reaction chamber containing biological reactants.

It is not intended that the present invention be limited by the nature of the flow-directing means used to convey fluids through the polymer channels of the present invention. In one embodiment, the present invention contemplates a device comprising a polymer channel, said polymer channel comprising one or more electrodes positioned such that they will be in contact with a liquid sample placed in said channel. The present invention also contemplates a method of conveying liquid in a microchannel, comprising introducing a liquid into an embodiment of such a device. In one embodiment, two electrodes are employed and a potential is applied between the two electrodes. At both ends of the electrodes, hydrolysis takes place and a bubble is generated. The gas bubble continues to grow as the electrodes continue pumping electrical charges to the fluid. The expanded bubble creates a pressure differential between the two sides of the liquid drop which eventually is large enough to push the liquid forward and move it through the polymer channel.

25 DEFINITIONS

The following definitions are provided for the terms used herein:

The term "biological reactions" is used herein to mean reactions involving biomolecules (and biological reactants) such as enzymes (*e.g.*, polymerases, nucleases, etc.) and nucleic acids (both RNA and DNA). Biological samples are those containing biomolecules, such proteins, lipids, nucleic acids. The sample may be from a microorganism (*e.g.*, bacterial culture) or from an animal, including humans (*e.g.* blood, urine, etc.). Alternatively, the sample may have been subject to purification (*e.g.* extraction) or other treatment. Biological reactions require some degree of biocompatibility with the device. That

is to say, the reactions ideally should not be substantially inhibited by the characteristics or nature of the device components. To this end, in one embodiment, the polymer-based technology of the present invention contemplates polymer-based microchannels comprising biocompatible polymers that do not inhibit biological reactions.

5 "Chemical reactions" means reactions involving chemical reactants, such as inorganic compounds. Again, it is desired that the reactions should not be substantially inhibited by the characteristics or nature of the device components. To this end, in one embodiment, the polymer-based technology of the present invention contemplates polymer-based microchannels comprising polymers that do not inhibit chemical reactions.

10 "Channels" are pathways through a medium (e.g., silicon) that allow for movement of liquids and gasses. Channels thus can connect other components, *i.e.*, keep components "in liquid communication." "Microdroplet transport channels" are channels configured (in microns) so as to accommodate "microdroplets." While it is not intended that the present invention be limited by precise dimensions of the channels or precise volumes for
15 microdroplets, illustrative ranges for channels and microdroplets are as follows: the channels can be between 0.5 and 200 microns in depth (preferably between 10 and 100 μm) and between 50 and 1000 μm in width (preferably 500 μm), and the volume of the microdroplets can range (calculated from their lengths) between approximately one (1) and (100) nanoliters (more typically between ten and fifty).

20 The term "conveying" is used herein to mean "causing to be moved through" as in the case where a microdroplet is conveyed through a transport channel to a particular point, such as a reaction region. Conveying can be accomplished via flow-directing means.

25 "Flow-directing means" is any means by which movement of liquid (e.g. a microdroplet) in a particular direction is achieved. A variety of flow-directing means are contemplated, including but not limited to pumps such as the "bubble pump" described herein. A preferred directing means employs a surface-tension-gradient mechanism in which discrete droplets are differentially heated and propelled through etched channels. For continuous flow of liquids, pumps are contemplated.

30 "Initiating a reaction" means causing a reaction to take place. Reactions can be initiated by any means (e.g., heat, wavelengths of light, addition of a catalyst, etc.). The present invention contemplates initiating reactions in the channels and reaction chambers fabricated according to the methods of the present invention.

"Liquid barrier" or "moisture barrier" is any structure or treatment process on existing structures that prevents short circuits and/or damage to electronic elements (*e.g.*, prevents the destruction of the aluminum heating elements). In one embodiment of the present invention, the liquid barrier comprises a first silicon oxide layer, a silicon nitride layer, and/or a second silicon oxide layer.

"Nucleic Acid Amplification" involves increasing the concentration of nucleic acid, and in particular, the concentration of a particular piece of nucleic acid. A preferred technique is known as the "polymerase chain reaction." Mullis, *et al.*, U.S. patents Nos. 4,683,195 and 4,683,202, hereby incorporated by reference, describe a method for increasing the concentration of a segment of target sequence in a mixture of genomic DNA without cloning or purification. This process for amplifying the target sequence consists of introducing a molar excess of two oligonucleotide primers to the DNA mixture containing the desired target sequence. The two primers are complementary to their respective strands of the double-stranded sequence. The mixture is denatured and then allowed to hybridize. Following hybridization, the primers are extended with polymerase so as to form complementary strands. The steps of denaturation, hybridization, and polymerase extension can be repeated as often as needed to obtain a relatively high concentration of a segment of the desired target sequence. The length of the segment of the desired target sequence is determined by the relative positions of the primers with respect to each other, and therefore, this length is a controllable parameter. By virtue of the repeating aspect of the process, the method is referred to by the inventors as the "Polymerase Chain Reaction" (hereinafter PCR). Because the desired segment of the target sequence become the dominant sequences (in terms of concentration) in the mixture, they are said to be "PCR-amplified."

DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic of one embodiment of an integrated microfluidic system using the technology of the present invention.

Figure 2 is a photograph of an electron micrograph of a polymer channel made according to the present invention. Figure 2 (a) is a top view and Figure 2 (b) is a cross-section.

Figure 3 is a schematic showing a simplified fabrication method of the present invention.

Figure 4 (a) shows the top view of a microchannel with toptype inlet fabricated using the methods of the present invention. Figure 4 (b) is a closeup electron-micrograph showing the three polymer construction of a channel made according to the methods of the present invention.

5 Figure 5 (a) shows the top view of a thermal cycling chamber constructed using the methods of the present invention. Figure 5(b) shows the cross-section of a similar PCR thermal cycling chamber showing the large volume of the cavity.

Figure 6 is a series of schematics showing the basic process steps of one embodiment of the fabrication method of the present invention.

10 Figure 7 is a schematic showing the simple suction pump.

Figure 8 is a schematic showing the cross-section of a pass-through valve implemented using the polymer based channel technology of the present invention.

Figure 9 is a schematic showing one embodiment of a bubble pump and capillary valve.

15 Figure 10 is a schematic showing liquid movement via the bubble pump and capillary valve.

Figure 11 shows another embodiment of a reaction chamber constructed using the methods of the present invention.

20 Figure 12 shows another embodiment of a thermocompression suction pump fabricated according to the methods of the present invention.

Figure 13 is a schematic showing one embodiment of the fabrication method for the bubble pump and capillary valve.

DESCRIPTION OF THE INVENTION

25 The present invention relates to polymer-based micro-electro-mechanical system (MEMS) technology suitable for the fabrication of integrated microfluidic systems, particularly medical and chemical diagnostics system, ink-jet printer head, as well as any devices that requires liquid-or gas-filled cavities for operation. The integrated microfluidic systems may consist of pumps, valves, channel, reservoirs, cavities, reaction chambers, mixers, beaters, fluidic interconnects, diffusers, nozzles, and other microfluidic components on
30 top of a regular circuit substrate.

Devices fabricated under this invention consist of two planar levels of functionality (See Figure 1). The top level consists of a polymer-based microfluidic plane, 30-50 μ thick

that is constructed on top of a regular silicon substrate. This plane of functionality contains all the microfluidic components of the diagnostic system such as channels, pumps, valves, thermal cycling reactor chambers, reservoirs, and electrophoresis stages. Beneath the microfluidic plane, the control, detection, drive and communication electronics are constructed in a conventional CMOS substrate chip. A series of holes are etched through the silicon substrate using anisotropic etching thus forming sample and reagent inlets and providing access to the microfluidic plane.

Figure 1(b) shows the proposed packaging assembly. First, access holes are ultrasonically drilled through a PGA ceramic package. The two-plane chip is mounted on the package and wire bonds are connected on the lead side for the electrical interconnects. The "fluidic" interconnects of the system are on the opposite side of the chip and hence do not interfere with the electrical connections. The chip cavity is next closed thus isolating the fragile electronic and microfluidic components from the surrounding environment.

Figure 2 shows SEM photographs of 25 μ -high, 3 mm-long polymer channels with frontside inlet. The details of the fabrication process are discussed in the Experimental section.

The proposed technology is suitable for the construction of a wide range of automated analytical instruments hence serving as a general testbench. When properly constructed, the testbench components can be configured to perform many different functions thus in essence forming a "fluidic microprocessor". The present invention contemplates the use of a common fluidic interconnect (*i.e.*, a fluidic bus) to move samples from any reservoir (or fluidic register) to any other, as well as allowing for controlled mixing. The set of mixing operations performed by the fluidic processor can be controlled by an external logic circuit.

The invention of polymer-based micromachining technology is vastly superior than those based on wafer bonding bulk micromachining, polysilicon surface micromachining, and hybrid plastic 'circuit board' technology in the following six categories. (a) The microfluidic plane fabrication is implemented by deposition of low-temperature layers that do not degrade or change the underlying circuit characteristics or its conventional process flow. (b) The fluidic-plane is fabricated using weak chemicals that do not attack the circuit plane in any way. Therefore, complex microfluidic devices can be fabricated using a regular MOS substrate plane containing the control circuitry, and a polymer-based microfluidic plane constructed on top of it. (c) Leak-tight channels are formed due to the conformality of the polymer deposition (a severe problem present in glass bonded devices): (d) Tall channels and

chambers of different heights can be easily fabricated. Unlike silicon-based films, these polymers can be quite thick with a thickness reported as high as 200 μ . Currently we can fabricate channels that range from 0.5 to 100 μ in height. (e) Very long channels can be fabricated with short etching times (also a problem with poly-Si). (f) Polymer channel walls do not have the severe surface adsorption problems observed in silicon and glass walls. (g) Polymer channels are optically transparent and are therefore are much simpler to test. (h) Its process simplicity and its capability of integrating individual fluidic components together make integrated microfluidic system possible. (i) Its batch-processing ability make microfluidic system inexpensive.

The following sections show several fabrication processes of microfluidic components. These microfluidic components and their process flows are presented to demonstrate the feasibility of polymer-based technology to fabricate the microfluidic systems. It is not intended that the present invention be limited by a particular type of fabrication process.

I. Selection of Polymers and Polymer Pairs

As noted above, it is not intended that the present invention be limited by the particular type of polymers. In one embodiment, polymer pairs are selected wherein the first polymer is soluble in a particular solvent, while the second polymer is not soluble in the same solvent. This permits the use of the polymer pair such that sacrificial etching with the solvent removes the first polymer but leaves the second polymer intact to serve as the polymer for the microchannel.

Selection of polymer pairs and solvents can readily be achieved by making reference to known solubilities of particular polymers with particular solvents. An example of such known solubilities is shown in the Table below (where "+" means soluble, "-" means insoluble, "(+)" means soluble at high temperatures). Specifically, illustrative solvents and polymers are given along with their corresponding δ_1 and δ_2 values.

| Illustrative Solubilities and Solubility Parameters of Polymers | | | | | |
|-----------------------------------------------------------------|------------|-------------------------------------|-----------------------------------------------|-----------------------------------------|----------------------------------------------------|
| Solvent | | Solubility of the Polymer | | | |
| | δ_1 | Poly(isobutene) $\delta_2 = 7.9$ | Poly(methyl methacrylate) $\delta_2 = 9.1$ | Poly(vinyl acetate) $\delta_2 = 9.4$ | Poly(hexamethylene adipamide) $\delta_2 = 13.6$ |
| Decafluorobutane | 5.2 | - | - | - | - |
| Neopentane | 6.25 | + | - | - | - |
| Hexane | 7.3 | + | - | - | - |
| Diethyl ether | 7.4 | - | - | - | - |
| Cyclohexane | 8.2 | + | - | - | - |
| Carbon tetrachloride | 8.62 | + | + | - | - |
| Benzene | 9.2 | + | + | + | - |
| Chloroform | 9.3 | + | + | + | - |
| Butanone | 9.3 | - | + | + | - |
| Acetone | 9.8 | - | + | + | - |
| Carbon disulfide | 10.0 | - | - | - | - |
| Dioxane | 10.0 | - | + | + | - |
| Dimethyl formamide | 12.1 | - | + | + | (+) |
| <i>m</i> -Cresol | 13.3 | - | + | + | + |
| Formic acid | 13.5 | - | + | - | + |
| Methanol | 14.5 | - | - | - | - |
| Water | 23.4 | - | - | - | - |

The utility of the solubility parameter approach is that δ (solubility parameter) can be calculated for both the polymer and solvent. There are three separate forces which together influence the δ 's numerical value. These include: 1) the number of dispersive forces present; 2) the number of dipole-dipole forces present; and 3) the number of hydrogen bonding forces present. As a first approximation and in the absence of strong interactions such as hydrogen bonding, solubility of a polymer in a solvent can be expected if $\delta_1 - \delta_2$ is less than 1.7 - 2.0, but not if appreciably larger.

Thus, as a general rule of thumb, a polymer is expected to be soluble in a solvent where δ_1 is approximately equal to δ_2 . Of course, it is contemplated that these values need

not be equal. The present invention contemplates using polymers and solvents where the values of δ_1 and δ_2 are within approximately 2.0 units (more preferably within approximately 1.0 unit and most preferably within approximately 0.5 units).

It is not intended that the present invention be limited to the solvents and polymers set forth in the above Table. Other solvents and polymers are contemplated. For example, soluble solutions of poly(styrene) ($\delta_2 = 9.3$), are readily obtained with butanone ($\delta_1 = 9.3$) and dimethylformamide ($\delta_1 = 12.1$), but not with acetone ($\delta_1 = 9.8$). In the liquid acetone, the acetone molecules form dimers through dipole-dipole interactions. In these dimers, the keto groups are shielded by the methyl groups, and so are no longer able to solvate the phenyl groups of the poly(styrene). The addition of the cyclohexane ($\delta_1 = 8.2$) decreases the tendency of the acetone molecules toward association, and thus frees keto groups for solvation. For the same reason, it is also possible to have 40% solutions of poly(styrene) in acetone. Butanone, on the other hand, is "internally diluted" by the additional CH_2 group, and is therefore a solvent over the whole concentration range.

Similar reasoning applies to mixtures of solvents. A solvent with a lower solubility parameter (*i.e.* than that of the polymer) can be combined with a solvent with a higher solubility parameter (*i.e.* than that of the polymer). Poly(acrylonitrile) ($\delta_2 = 12.8$), for example dissolves in both dimethylformamide ($\delta_1 = 12.1$) and malodinitrile ($\delta_1 = 15.1$), but not in a mixture of the two. In some embodiments, the present invention contemplates etching with solvent mixtures.

II. Basic Polymer Process: Polymer Channels

The basic fabrication process begins with a conventional silicon CMOS processed substrate, as shown in Figure 3. In this figure, inlet and outlet are etched from the front side. However, backside inlet and outlet can easily be made by etching holes into the substrate from the backside using an anisotropic etchant such as ethylenediamine pyrazine (EDP), tetramethylammonium hydroxide (TMAH) or even XeF_2 stopping at the passivation oxide or nitride (also see Section III). Other alternatives on passivation layer includes oxide/nitride/oxide and low stress silicon-rich silicon nitride. Next, the microfluidic plane is constructed using the simplified process shown below. First a thick polymer layer is deposited and photolithographically defined onto the substrate with the thickness required for the channel height (0.5-100 μ). Next a second polymer is deposited serving as the walls of the channels. The second polymer is next etched defining the extent of the channel walls. Holes

to polymer 1 can be etched either from the front or through the backside by plasma etching the passivation oxide (see Section III). Polymer 1 is now sacrificially etched leaving a channel behind. In some cases where polymer 2 may react with polymer 1, a third material serves as a barrier layer, is deposited in between polymer 1 and polymer 2. The barrier layer has to be relatively conformal to provide a complete physical contact of polymer 1 from polymer 2.

Figure 4 is an example of a simple polymer channel: Figure 4(a) shows the top view of a 100μ wide, 25μ -high channel with toptype inlet fabricated using this process. Channels as long as 3mm are completely sacrificially released in under 20 minutes time. These channels are optically clear. Figure 4(b) shows a closeup SEM showing the three polymer construction of a 15μ -high channel with 40μ -thick walls.

In this example, photodefinable polyamide is used as polymer 2, vapor-deposited p-xylylene as the thin intermediate barrier material, and thick photoresist as polymer 1. The details of embodiments of the fabrication process are set forth in the Examples. It is not intended that the present invention be limited by the particular type of polymers. Polymers include, but are not limited to, photoresist, polyamide, benzocyclobutene, polydimethylsiloxane, vapor-deposited p-xylylene, pTEE, PMMA, p-HMDS, polypropylene, starch-based polymers, epoxy, and acrylics. In addition, it is not intended that the present invention be limited by the particular barrier layer. The barrier layers include, but are not limited to, metal, stack of different metals, pTFE, polymers, silicon-based materials, and other inorganic materials. Fluidic Interconnects can also easily be fabricated as shown in Example 2 (below).

III. Fabricating Reservoirs, Mixers, Reaction Chambers, Cavities

Reservoirs, mixers, reaction chambers, and any cavities can be formed by proper enlargement of the channels while heaters, detectors, and active circuits reside on the CMOS plane below. Figure 5 shows an example of a reaction chamber. The details of one embodiment of the fabrication process are set forth in the Examples. Figure 5a shows the top view of 1 mm^2 , $25\mu\text{m}$ -high thermal cycling chamber constructed using this process. The dots on the cavity are posts periodically spaced inside the cavity which enhance mixing and stiffen the cavity to prevent it collapse. The cavity is connected at both ends with short channels leading to top inlets and outlets. Figure 5(b) shows the cross-section of a similar PCR thermal cycling chamber showing the large volume of the cavity. Ink-jet printer head

can be fabricated similar to the PCR reactor except that there are arrays of etch holes (circular or square) on the structural polymer. Instead of forming post in the large cavity, internal walls are built so that each etch hole is isolated and is connected to an internal reservoir, which stores ink. Under each isolate cavities, heaters are placed or suspended on tope of the substrate.

IV. Fabricating Actuators

The same process also allows the fabrication of actuators such as valves and pumps. The polymer process must include the following layers: (1) a sacrificial polymer layer for forming cavities and channels; (2) a thick elastic structural polymer layer for forming elastic diaphragms needed in pumps and valves. This thin polymer can also serve as a barrier layer in some cases; (3) a thick structural polymer layer for construction of thick channel walls and bossed diaphragms; and (4) a metal layer that can carry current either embedded between (2) and (3) or on top of layer (3). Figure 6 shows the basic process steps carried out to fabricate the actuator.

The process begins with a conventional CMOS, bipolar, or BiCMOS substrate passivated by a layer of silicon dioxide. Metal lines can be present on the circuit side if desired. The next step in the process consists of the opening of holes on the backside oxide by plasma etching. These holes will provide access to the microfluidic polymer plane. After this step, the circuit substrate is immersed in a silicon rich TMAH solution that anisotropically etches the substrate all the way to the passivation oxide layer. The cavities formed by this etch are bounded by the 111 crystal planes of the substrate. The silicon saturated TMAH solution will not attack any aluminum wires exposed on the surface [U. Schankenberg *et al.*, "TMAHW Etchants for Silicon Micromachining," in *Transducers '91*, pp. 815-818 (1991)].

After rinsing and drying the substrates, a passivation layer is deposited on top of the circuits and subsequently patterned. The passivation layer is needed if the system being built must handle fluids that contain mobile ions such as sodium ions and potassium ions (many biochemical reactions require weak KCl buffer solutions) which can easily diffuse through the oxide passivation of the circuit plane. Several types of passivation layers can be used (or even none). Conventional materials such as sputtered SiN serve the purpose quite well. Polymers can also be used as a barrier to the contaminant diffusion. The barrier layer is next photolithographically defined and etched on the areas leading to the backside inlet and metal contact areas.

Wafers that have reached this state are ready for the construction of the microfluidic plane. First a thick polymer 1 layer is deposited and etched on top of the substrate. This thick polymer serves as a spacer layer that determines the height of channels and microfluidic components. Multiple thicknesses on the same wafer can be obtained through time etching or multiple depositions. The range of thicknesses for this polymer is between 0.5-200 μ . Next a thin layer of polymer (polymer 2) 0.5-2 μ thick is deposited uniformly onto the wafer. Polymer 2 serves as a thin structural layer that is easily deflected, and as a barrier layer in some cases. Its main purpose is for the fabrication of flexible membranes required by the pumps and valves described earlier. Next, a thin layer 1-2 μ of aluminum is evaporated on top of polymer 2 and it is photolithographically defined to form parallel conductors and interconnects used in the fluidic actuators. The process is followed by the deposition and patterning of a thick polymer (polymer 3) that provides structural support for the channels and microfluidic component walls. Next holes are opened on the thin polymer 2 layer leading to bonding pads on the circuit plane and also providing access to polymer 1 if desired from the front side. At this point the remainder passivation oxide that separates polymer 1 from the backside inlets is etched by plasma etching. In the last step of the process, polymer 1 is sacrificially etched thus releasing the channels and fluidic actuators. The chips are next mounted on a ceramic package and the electrical leads are formed by wire bonding. As an example, polymer 1 can be photoresist, polymer 2 can be p-xylylene, and polymer 3 can be polyamide.

Droplets of the samples must be moved to the various parts of the system in order to perform various tests on the fluidic chip. A thermocompression suction pumps that create a pressure differential between the two sides of the liquid drop can be used. A simple suction pump can be constructed as shown in Figure 7. The pump basically consists of a heater and a valve. This device is constructed with an additional thin polymer layer and an embedded metallization inserted on the microfluidic plane. The construction of this type of pump is thus entirely compatible with the polymer-based technology. This pump basically consists of a heater constructed on a polysilicon heater constructed on the MOS plane placed under the polymer channel, and an exhaust valve. The exhaust valve consists of an enlarged version of the channel with a central outlet. On top of the polymer valve, a series of parallel aluminum wires are patterned. The aluminum wires are placed between a thin polymer and a thick one thus forming a boss region and a diaphragm. This valve is magnetically actuated upon application of a transversal magnetic field B (through an external permanent magnet). The

valve either closes or opens depending on the direction of the current I on the parallel conductors. Magnetic actuation was chosen for the valve because the tall channels generated by the polymer-based process have very high pull-in voltages hence rendering electrostatic actuation impractical.

5 The thermocompression pump operates as follows: first, the exhaust valve is opened and the heater is powered up. Next the valve is closed and the heater is turned off thus forming a partial vacuum on the channels as the trapped air cools down. This partial vacuum propels the drop forward until the pressure difference disappears. The cycle is repeated for continuous pumping. Propulsion of the droplet in the reverse direction can also be achieved
10 by expanding the gas rather than contracting it. This type of simple pump can generate pneumatic pressure differences as high as 0.5μ , well above the threshold needed for the onset of motion of droplets in capillaries. If the pneumatic drop motion mechanism is used, *pass-through valves* are needed into the system. These valves basically constrict the channels at various points in the system thus acting as gates that block the passage of liquids. Pass-
15 through valves are necessary to impede the continuous drawing of liquids onto the capillary. This situation occurs due to the fact that when droplets are moved inside the capillary channels, they form a partial vacuum behind them which can in turn move drops on other parts of the system. Pass through valves impede the entrance of these drops onto places where there exist temporary vacuum pressure differences. It is also important to point out that once a channel
20 is blocked, it is necessary to open an exhaust valve (such as those made for the thermocompression pump) attached to the same end as the blocking valve if additional liquid drop motion is desired. The exhaust valve provides an additional inlet that impedes the formation of a vacuum behind the moving drop that would ultimately stop additional drop motion.

25 This brings the important point that pumping of discrete drops can only be accomplished when one of channel ends is open to the environment. This problem has been pointed out by Anderson (*supra*) who has proposed the use of permeable membranes to eliminate this problem. Figure 8 shows the cross-section of a pass-through valve implemented using the polymer based channel. The valve basically consists of a flat round segment of an
30 enlarged channel that is constructed in its collapsed form by the deliberate removal of polymer 1. A patch of polymer 3 (Teflon) is placed under the valve such that polymer 2 does not stick to the surface. The valve is opened or closed by applying a current to the

conductors above the pass-through valve which buckle the diaphragm upward thus opening the valve.

V. Bubble Pumps and Capillary Valves

5 As noted above, it is not intended that the present invention be limited by the nature of the flow-directing means used to convey fluids through the polymer channels of the present invention. In one embodiment, the present invention contemplates a polymer channel comprising one or more electrodes in contact with the liquid sample. A schematic of one embodiment of the bubble pump and capillary valve is shown in Figure 9. The bubble pump
10 comprises a polymer channel with several electrodes (e.g. Ti/Pt electrodes) in contact with the liquid sample. When coupled with the capillary valve, the bubble pump can actuate a certain quantity of fluidic samples along the polymer chip. The capillary valve is essentially a narrow section of a polymer channel. In operation, the fluidic sample is first injected in the inlet reservoir. As soon as the fluid is loaded, it moves in the channel by capillary force.
15 The fluid then passes the narrow section of the channel but stops at the edge where the channel widens again (see Figure 10A). After the fluidic sample is loaded, a potential is applied between two electrodes. At both ends of the electrodes, hydrolysis occurs and bubble is generated. The bubble keeps on growing as the electrodes continue pumping electrical charges to the fluid (Figure 10B). The expanding bubble then creates a pressure differential
20 between the two sides of the liquid drop, which eventually large enough to push the liquid forward (Figure 10C).

The combination of bubble pump and capillary valve is an excellent fluid propelling device. This actuating device does not require any moving parts and is easy to fabricate. In addition, the device produces a well-controlled fluid motion, which depends on the bubble
25 pressure. The bubble pressure is controlled by the amount of charges pumped by the electrodes. Furthermore, the power consumption of the device is minimal.

EXPERIMENTAL

The following examples serve to illustrate certain preferred embodiments and aspects
30 of the present invention and are not to be construed as limiting the scope thereof.

EXAMPLE 1

This example describes one embodiment of the fabrication method of the present invention. More specifically, this example describes one embodiment of the process flow for channels and cavities with frontside inlets and outlets.

- 5 The process starts with a 4 inch silicon wafer. Thereafter, the steps are as follows:
0. (Optional) Deposit 2 μ -thick p-xylylene with primer.
 1. HMDS is spread at 200 rpm for 16s, and spun at 4000rpm for 30s.
 2. Photoresist (AZP4620) is spread at 200rpm for 16s. and spun at 750rpm for 50s (about 20 μ -thick). Experiments reveal that this resist does not stick too well with silicon
10 substrate without applying HMDS. For some other resist, HMDS may not be applied.
 3. Remove the resist beads which reside on the edge of the wafer using Q-tip soaked with acetone. This step is necessary because these beads will glue to the mask plate during mask aligning.
 4. Soft baked on a hot plate for 2 mins. at 130°C. Lower temperature with longer
15 bake time should also work.
 5. Patterned and exposed at intensity of 1250 ml/cm².
 6. Developed for 16 mins in AZ312: H2O=1:1.
 7. Hard baked at 130° for 3 mins.
 8. Plasma etching using O₂ at 80W: 250mT for 2 mins. Longer etching time may
20 burn the resist.
 9. Deposit 2 μ m-thick p-xylylene without applying primer. The p-xylylene will crack if it is too thin. and resist will crack if primer is applied. Without primer. the adhesion between p-xylylene and silicon substrate is not too good.
 10. Plasma etching using O₂ at 80W for 2 mins. This dry etching is necessary to
25 improve the adhesion between parylene and polyamide.
 11. Polyamide (Polyamide 7020 from OCG) is spread at 200rpm for 10s. and spun at 2500rpm for 10s (about 40 μ -thick).
 12. Soft bake at 90°C for 2 mins, followed by baking at 110° for 7 mins..
 13. Pattered and exposed at intensity of 350ml/cm².
 - 30 14. Bake at 105° C for 1 mins.
 15. Let it rest for 30 mins.
 16. Develop (QZ2501 from OCG) for 6 mins. Agitate.

17. Rinse (QZ3512 from OCG) for 2 mins. Agitate. If some white residual is observed, put the wafer to the developer.
18. Blow dry.
19. Repeat Step 2 to 6. No HMDS is applied because adhesion between p-xylylene
5 and polyamide is strong enough.
20. Etching p-xylylene: Plasma etching using O_2 at 250W, 250mT for 20 mins.
21. Sacrificial release: Immersed into hot Acetone for 20 mins.
22. Rinse with IPA and water.
23. (Optional) Final Cure 250° for 30 mins. Higher temperature may burn p-
10 xylylene.

EXAMPLE 2

This example describes another embodiment of the fabrication method of the present invention. More specifically, this example describes one embodiment of the process flow for
15 fluidic interconnect. The process starts with a 4 inch silicon wafer. Thereafter the steps are as follows:

1. Repeat Step 11 to 18 from Example 1.
2. Repeat Step 2 to 6 from Example 1.
3. Repeat Step 9 to 22 from Example 1.
- 20 4. (Optional) Final Cure 250° for 30 mins. Higher temperature may burn p-xylylene.

EXAMPLE 3

In this example, another embodiment of a reaction chamber is constructed using the
25 methods of the present invention. The fabrication process is same as in Example 1 (above). Figure 11 shows the resulting reaction chamber with one supporting post. The reaction chamber is approximately 1mm long, 1mm wide and 20 μ m high.

EXAMPLE 4

30 In this example, another embodiment of a thermocompression suction pump is fabricated according to the methods of the present invention. A thermocompression suction pump is fabricated (Figure 12) that is similar to the one described in Figure 7 of the patent. Figure 12 shows a polymer valve of 1mm in diameter with a 30 μ m thick boss of 320 μ m in

diameter. The valve orifice is 80 μm in diameter. A combination of chromium and gold of 50 μm -wide are placed on top of the 4 μm -thick p-xylylene diaphragm. The polymer valve is connected to a stand channel of 100 μm wide.

5

EXAMPLE 5

In this example, one embodiment of the fabrication method for the bubble pump and capillary valve is described. Figure 13 is a schematic showing the embodiment of the fabrication method for the bubble pump and capillary valve.

The process begins with a 100 mm p-type silicon substrate with a 0.7 μm layer of thermally grown silicon dioxide. The hydrolysis electrodes are next formed by evaporating a thin layer of 20 nm of Ti followed by a 30 nm layer of Pt and patterned by liftoff using a 3 μm of Shirley 1827 photoresist and acetone. A uniform thin layer of p-xylylene (Specialty Coating Services, parylene-C) 2 μm -thick is vapor deposited at room temperature on the oxidized substrates. The p-xylylene layer is next roughened with a 100W, 300mT O_2 plasma for 2 minutes to improve the adhesion of the subsequent polymer layer. A 10 μm -thick layer of photosensitive polyamide (OCG Probimide 7020) is next spin-cast at 7000 rpm for 10 sec. serving as a stop. The sample is soft baked at 90°C for 2 min. followed by 110° for 7 min. The soft baked polyamide is next exposed and patterned with a dose of 350mJ/cm² followed by a bath in OCG QZ2501 developer for 5 min and a 1 min. rinse in QZ3512. Next, a second 2 μm layer of p-xylylene is deposited on top of the polyamide and selectively etched on the Pt electrode areas with a 250W, 50mT O_2 plasma for 30 min. After that, the polymer channel is ready to be constructed. First, a 20 μm -thick sacrificial layer of AZP4620 (Hoechst) photoresist is spin cast at 750 rpm for 50 sec. and soft baked at 130° and exposed using a dose of 1750mJ/cm² to define the channel area. A second partial exposure of 250mJ/cm² is performed to define the narrow section of the channel, followed by a 10 min development in AZ 312. After that, the wafer is hard baked at 130°C, followed by a short O_2 plasma descum. A third 2 μm thick layer of p-xylylene is deposited which completely seals the resist layer and prevents the subsequent polyamide solvent from attacking the soft sacrificial resist. The top p-xylylene is next roughened with O_2 plasma and the top structural layer is constructed by spin-casting and patterning a 30 μm thick of photoresist polyamide as described earlier. This is followed by an O_2 plasma descum and a final 1 μm p-xylylene deposition. Access holes to the sacrificial resist are patterned using a 20 μm -thick layer of resist (AZP4620) and etched in a 250 W, 50mT, O_2 plasma for 35 min. that removes the two

p-xylylene layers on top of the sacrificial resist layer and at the same time the three p-xylylene layers on top of the platinum electrodes for electrical contact. The masking resist and the sacrificial resist layer are both removed in a warm bath of acetone for about 50 min. followed by a rinse in isopropyl alcohol and DI water.

5

From the above, it should be clear that the polymer-based technology of the present invention provides a micromachining technology that allows for fabrication of channels with a flexibility in cross section and channel length with virtually no loss in system performance.

10 In addition, the polymer technology of the present invention is low cost and does not require specialized equipment.

CLAIMS

1. A method for fabricating microchannels, comprising the steps:
 - a) providing a substrate, said substrate having upper and lower surfaces;
 - 5 b) depositing a first polymer layer on said upper surface of said substrate, said first polymer layer having i) a lower surface contacting said upper surface of said substrate and ii) an upper surface;
 - c) depositing a second polymer layer on said upper surface of said first polymer layer, said second polymer layer having i) a lower surface contacting said upper surface of said first polymer layer and ii) an upper surface; and
 - 10 d) sacrificially etching said first polymer layer under conditions such that said second polymer layer comprises walls of a microchannel.
2. The method of Claim 1, wherein said substrate is a silicon substrate.
- 15 3. The method of Claim 1, further comprising, prior to step (c) the step of photolithographically defining said first polymer layer under conditions such that said first polymer layer has a desired thickness.
- 20 4. The method of Claim 3, wherein said desired thickness of said first polymer layer is between 0.5 and 200 μ .
5. The method of Claim 1, further comprising, prior to step (d) the step of photolithographically defining said second polymer layer.
- 25 6. The method of Claim 1, further comprising, after step (d) the step (e) of etching openings in said walls of said microchannel.
7. The method of Claim 6, further comprising after step (d) and before step (e) the step
- 30 of depositing a third polymer layer on said upper surface of said second polymer layer.
8. The method of Claim 1, wherein said first polymer and said second polymer are selected from the group consisting of photoresist, polyamide, benzocyclobutene,

polydimethylsiloxane, vapor-deposited p-xylylene, pTFE, PMMA, p-HMDS, polypropylene, starch-based polymers, epoxy, and acrylics.

9. A method for fabricating microchannels, comprising the steps:

- 5 a) providing a silicon substrate, said silicon substrate having upper and lower surfaces;
- b) depositing a first polymer layer on said upper surface of said silicon substrate, said first polymer layer having i) a lower surface contacting said upper surface of said silicon substrate and ii) an upper surface;
- 10 c) photolithographically defining said first polymer layer under conditions such that said first polymer layer has a desired thickness;
- d) depositing a second polymer layer on said upper surface of said first polymer layer, said second polymer layer having i) a lower surface contacting said upper surface of said first polymer layer and ii) an upper surface; and
- 15 e) sacrificially etching said first polymer layer under conditions such that said second polymer layer comprises walls of a microchannel.

10. The method of Claim 9, wherein said desired thickness of said first polymer layer of step (c) is between 0.5 and 200 μ .

20

11. The method of Claim 9, further comprising, prior to step (e) the step of photolithographically defining said second polymer layer.

12. The method of Claim 1, further comprising, after step (e) the step (f) of etching
25 openings in said walls of said microchannel.

13. The method of Claim 12, further comprising after step (e) and before step (f) the step of depositing a third polymer layer on said upper surface of said second polymer layer.

30 14. The method of Claim 9, wherein said first polymer and said second polymer are selected from the group consisting of photoresist, polyamide, benzocyclobutene, polydimethylsiloxane, vapor-deposited p-xylylene, pTFE, PMMA, p-HMDS, polypropylene, starch-based polymers, epoxy, and acrylics.

15. A method for fabricating microchannels, comprising the steps:
- a) providing a silicon wafer, said silicon wafer having upper and lower surfaces;
 - b) depositing a first layer of a first polymer on said upper surface of said silicon wafer, said first polymer layer having i) a lower surface contacting said upper surface of said silicon wafer and ii) an upper surface;
 - c) depositing a second polymer layer on said upper surface of said first layer, said second polymer layer having i) a lower surface contacting said upper surface of said first layer and ii) an upper surface;
 - d) photolithographically defining said second polymer layer under conditions such that said second polymer layer has a thickness between 0.5 and 200 μ ;
 - e) depositing a second layer of said first polymer on said upper surface of said second polymer layer, said second layer of said first polymer having i) a lower surface contacting said upper surface of said second polymer layer and ii) an upper surface;
 - f) sacrificially etching said second polymer layer under conditions such that said first and second layers of said first polymer comprise walls of a microchannel, said microchannel having a height defined by said thickness of said second polymer layer of step (d); and
 - g) etching one or more openings in said walls of said microchannel.
16. The method of Claim 15, further comprising after step (e) and before step (f) the step of depositing a layer of a third polymer on said upper surface of said second layer of said first polymer.
17. The method of Claim 16, wherein said first and second layers of said first polymer comprise vapor-deposited p-xylylene.
18. The method of Claim 17, wherein, at step (g), first and second openings are etched, said first opening serving as an inlet and said second opening serving as an outlet.
19. The method of Claim 18, wherein said openings are etched from said lower surface of said silicon wafer into said lower surface of said first layer of said first polymer.

20. The method of Claim 18, wherein said openings are etched from said upper surface of said layer of said third polymer into said upper surface of said second layer of said first polymer.
- 5 21. A device, comprising a polymer channel comprising one or more electrodes positioned such that they will be in contact with a liquid sample placed in said channel.
22. The device of Claim 21, wherein said polymer channel comprises two electrodes.
- 10 23. A method of conveying liquid in a microchannel, comprising introducing a liquid into the device of Claim 22.
24. The method of Claim 23, wherein a potential is applied between the two electrodes under conditions such that said potential results in the generation of a gas bubble large enough
- 15 to move at least a portion of said liquid in said polymer channel.

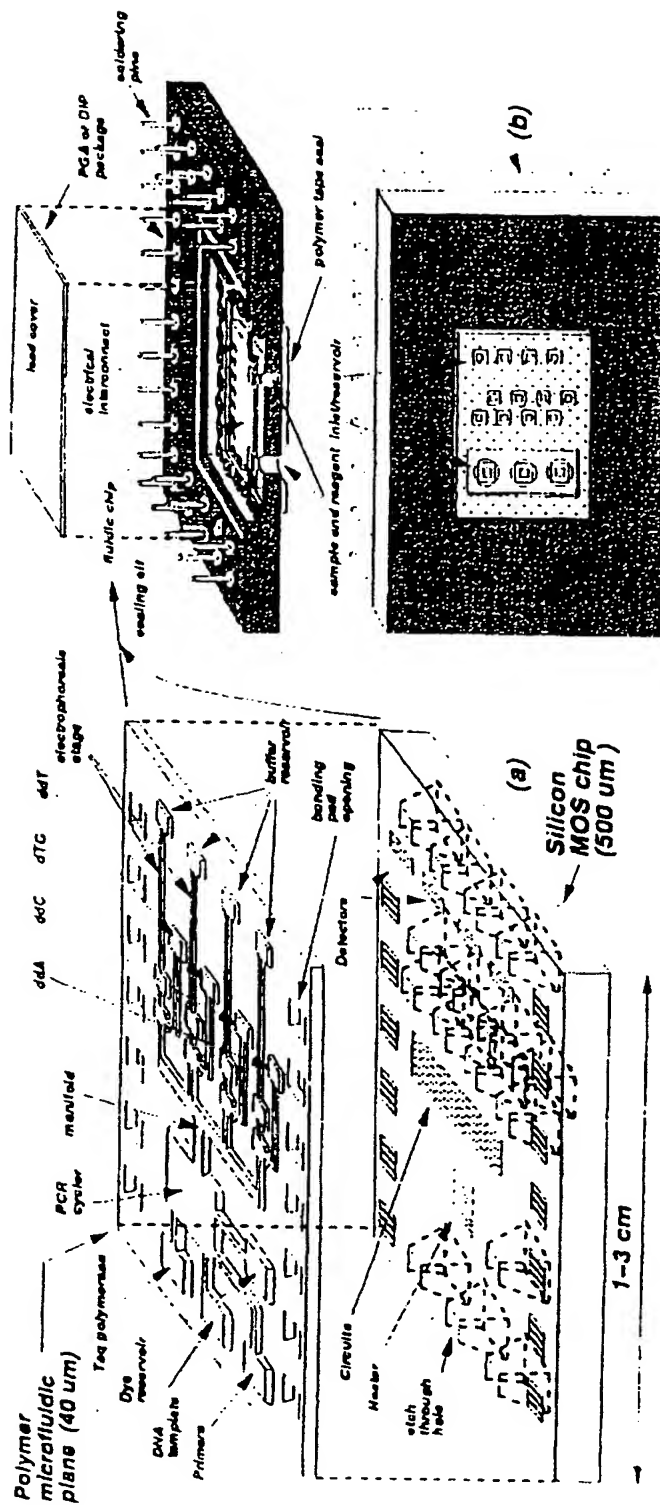


Figure 1: (a) The polymer fluid channels and reservoirs are constructed by deposition of plastics on top of a silicon MOS control chip. Etch-through holes in the silicon substrate serve as funnel-like inlets and reservoirs for the sample, reagents and buffer solutions. (b) Fluidic chip is mounted on a PGA or MCM package that isolates fluidic and electrical interconnect. Some of the sample inlets are sealed to serve as reagent reservoirs

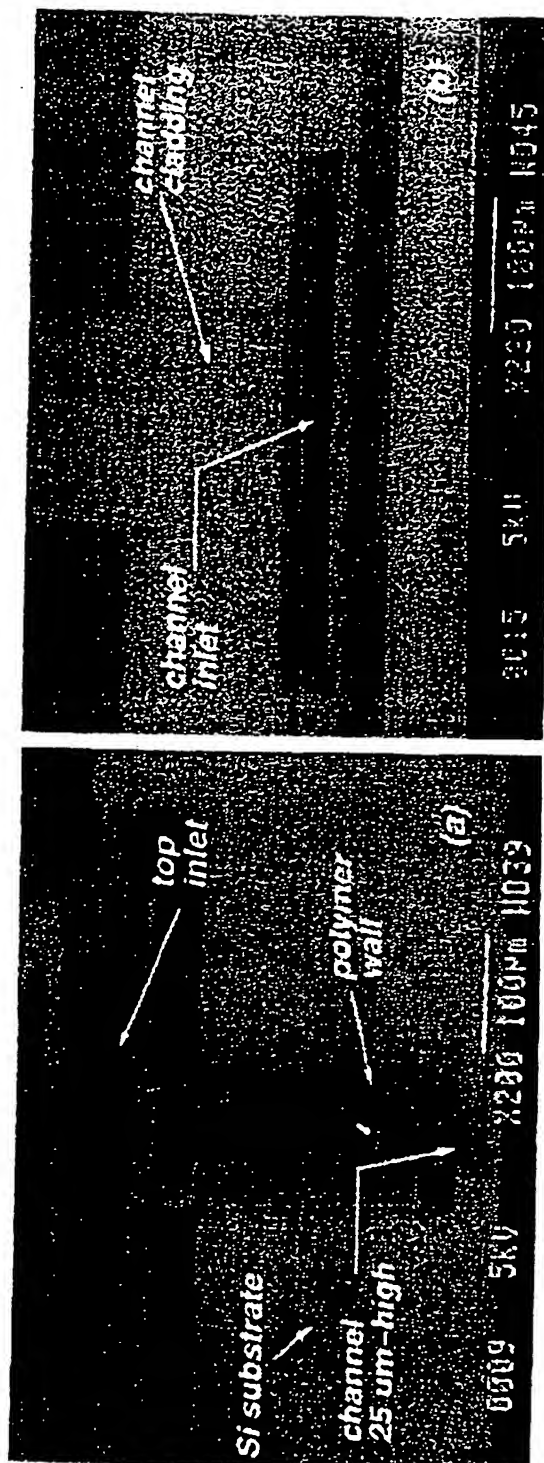


Figure 2: Top view and cross-section (a) of example polymer channel with front side inlet (b) formed on top of a regular Si substrate. Channel heights can be adjusted between 0.5-100 μm .

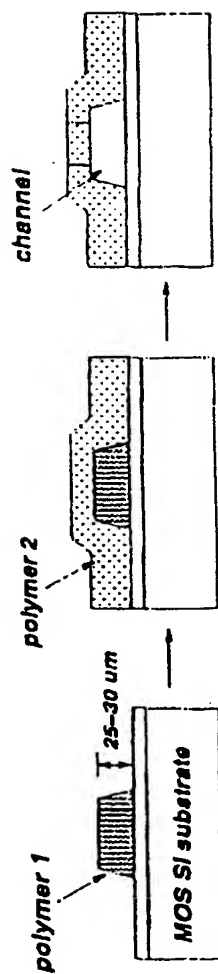


Figure 3: Simplified fabrication process for plastic channels.

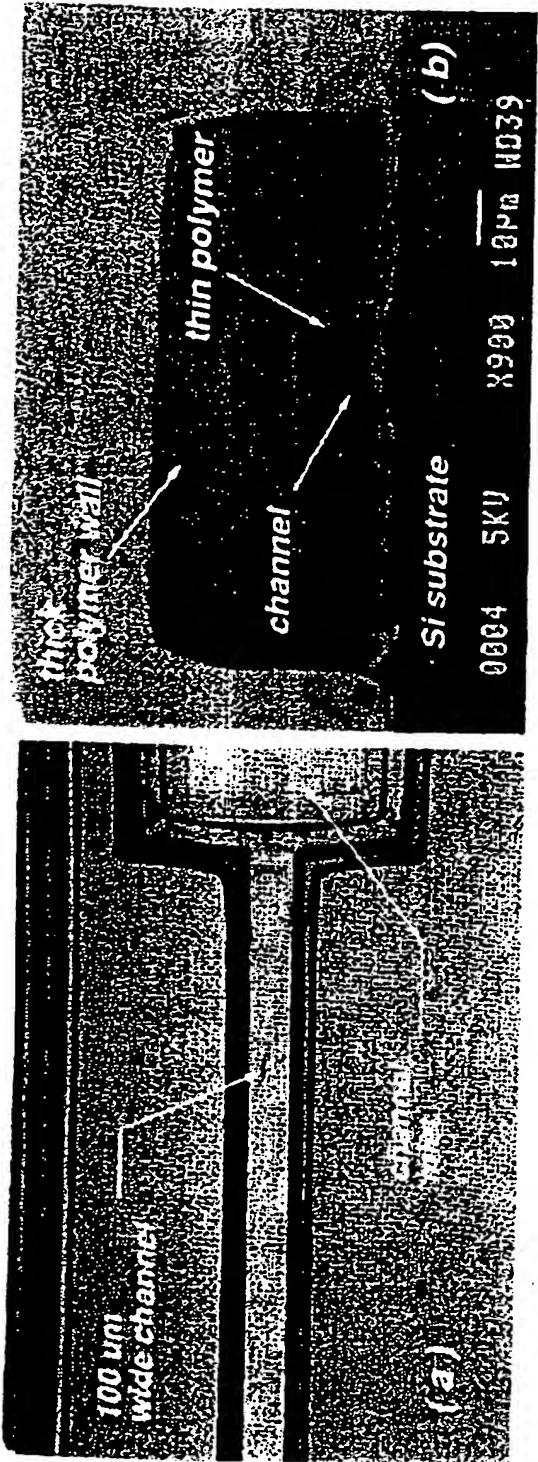


Figure 4: (a) Top view of example three-polymer channel 100 μm wide and 25 μm -thick with front side inlet. (b) closeup cross-section showing the three-polymer construction of the channels.

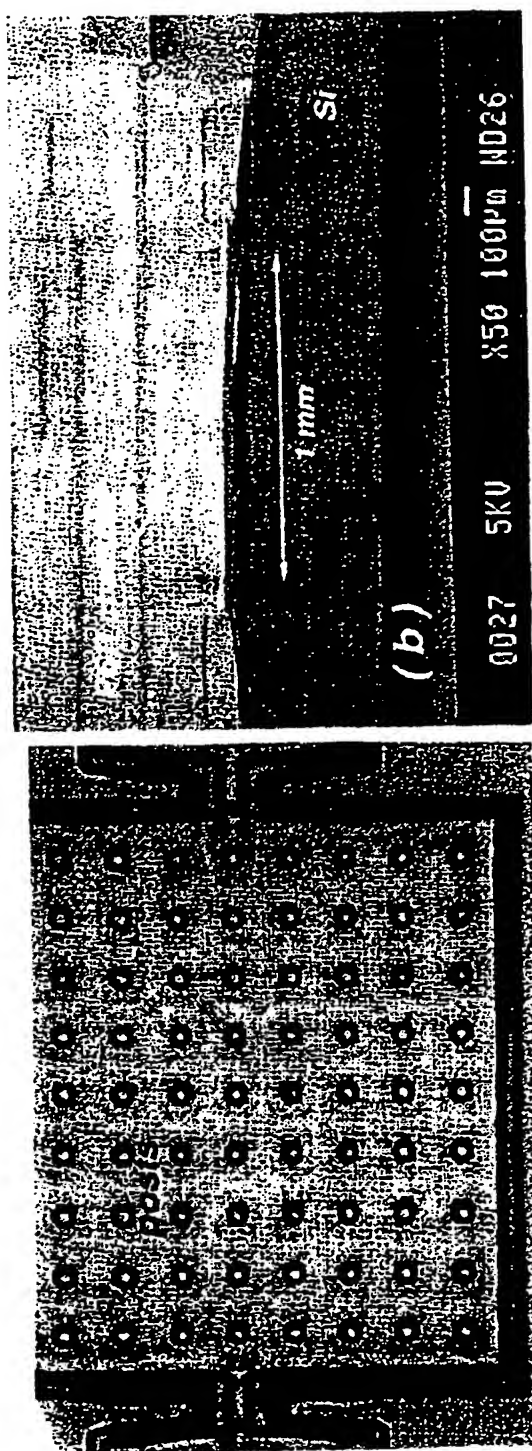


Figure 5: (a) Top view of 1 mm² thermal cycling chamber (b) cross-section of 25 μm-high, 1 mm² polymer PCR chamber fabricated on top of a silicon wafer.

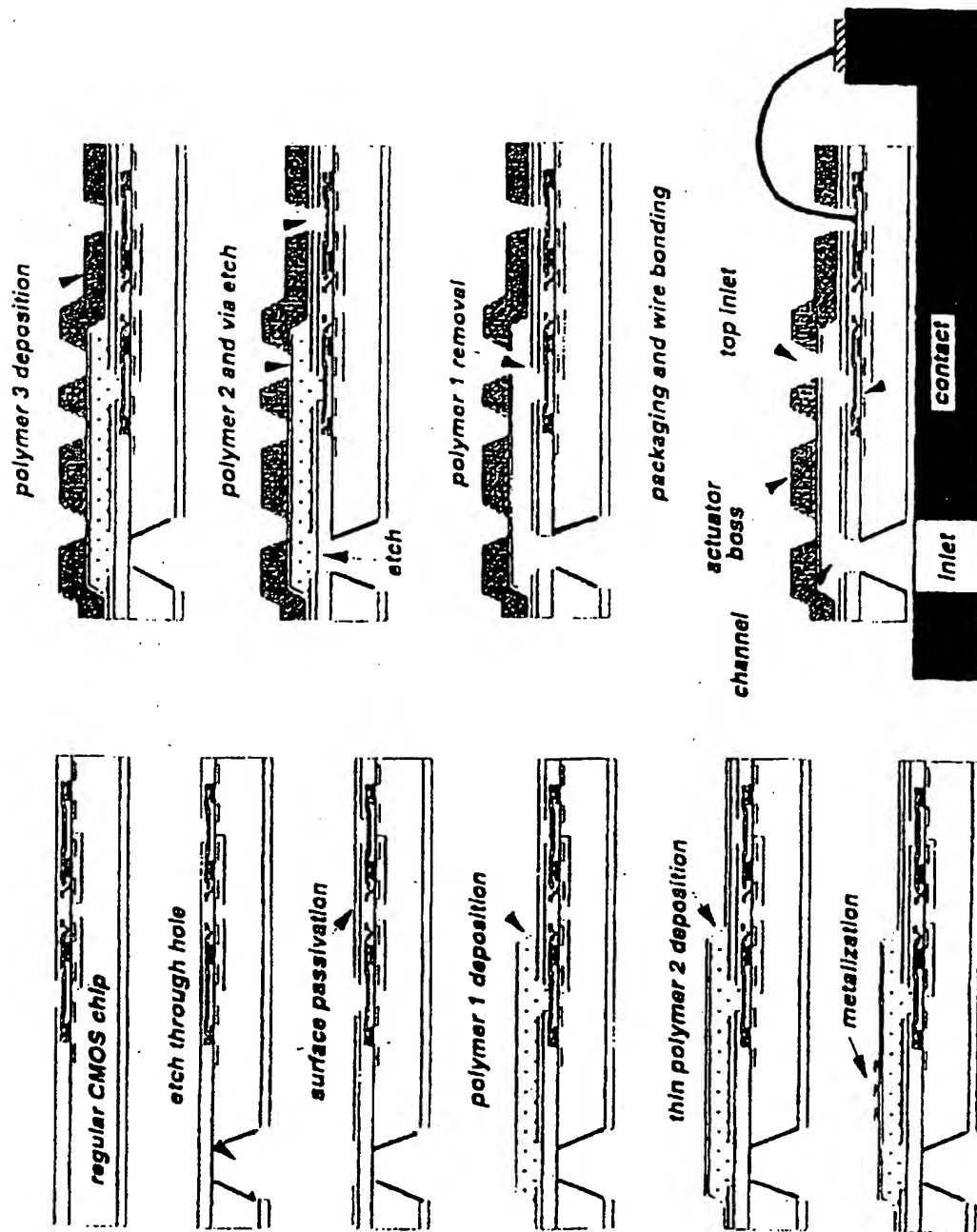


Figure 6: Simplified 3-level polymer process with embedded metalization. This process requires four lithographic masks and is capable of constructing all the microfluidic parts shown in this proposal. The figure shows circuits, backside and front inlets, actuators, channels, and bonding wires.

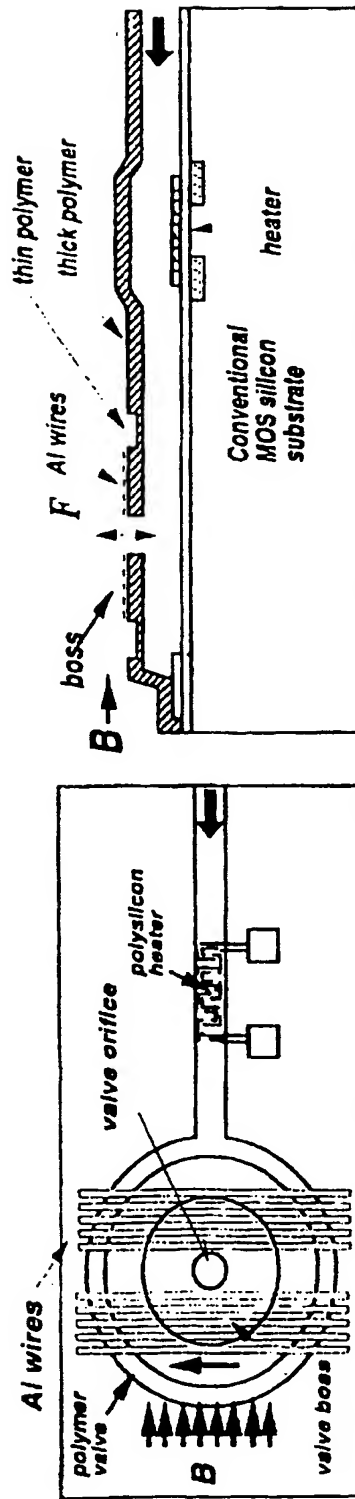


Figure 7: Polymer magnetically activated thermocompression suction pump

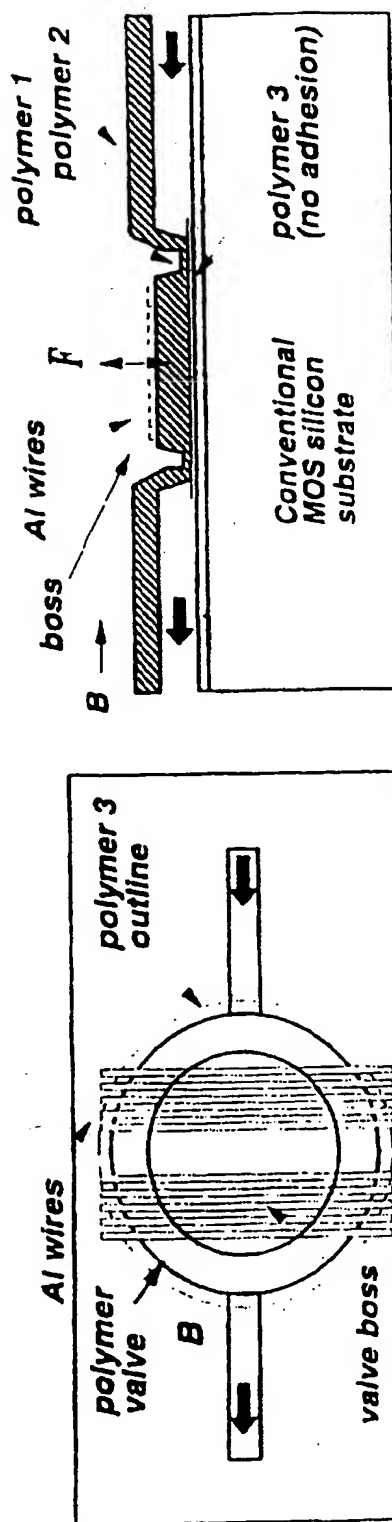


Figure 8: Pass-through valve. The valve is normally closed and opens when the diaphragm is buckled upwards

FIGURE 9

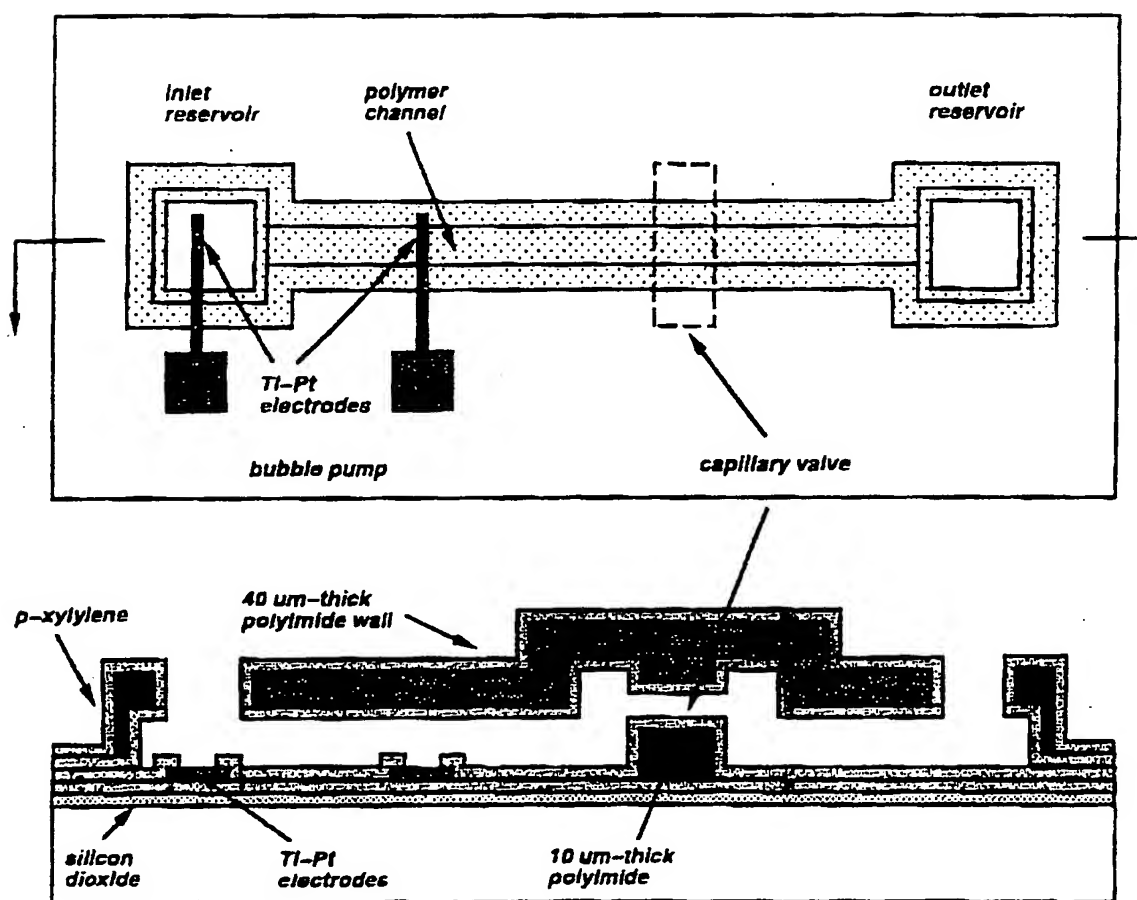


FIGURE 10

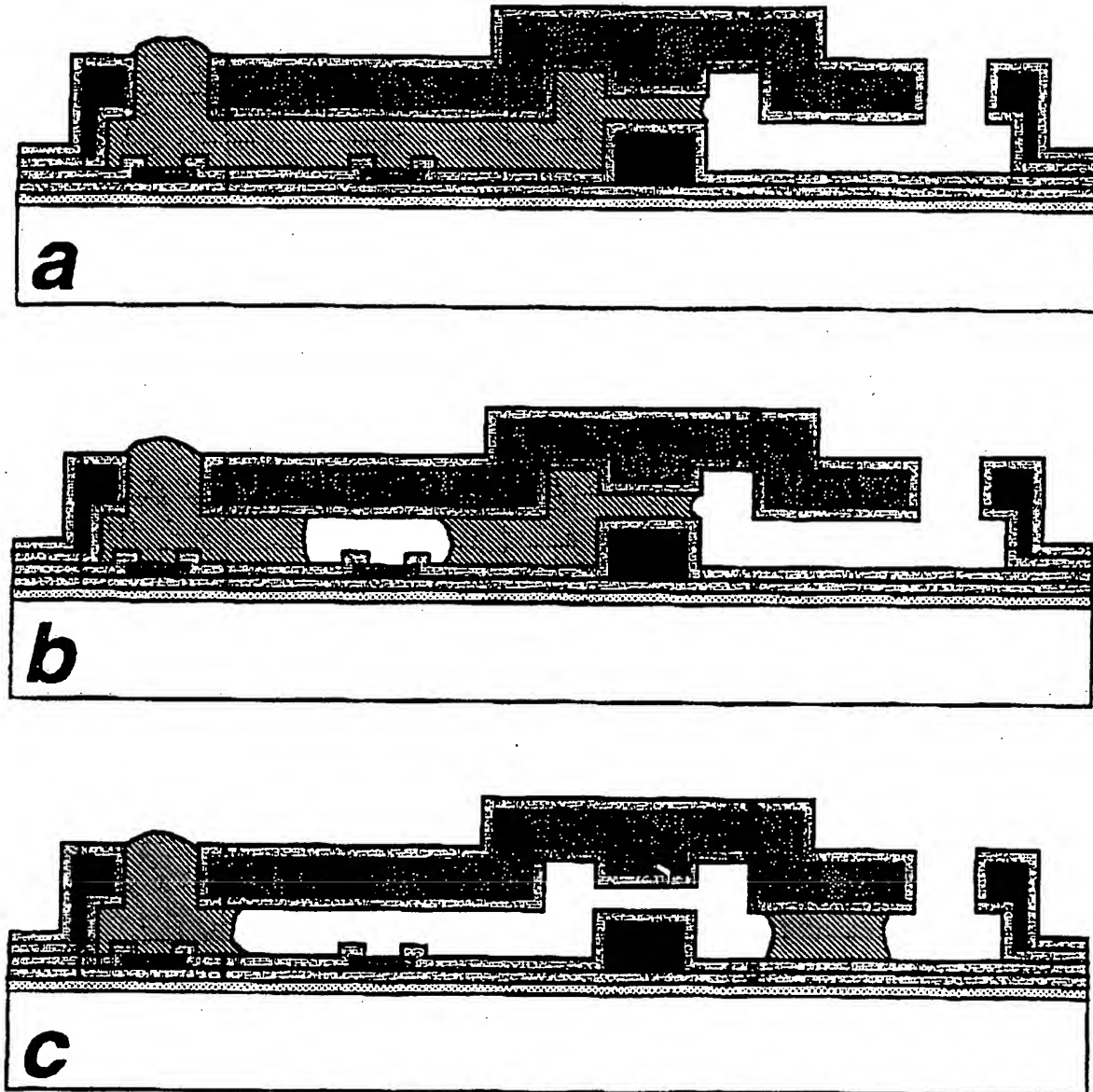
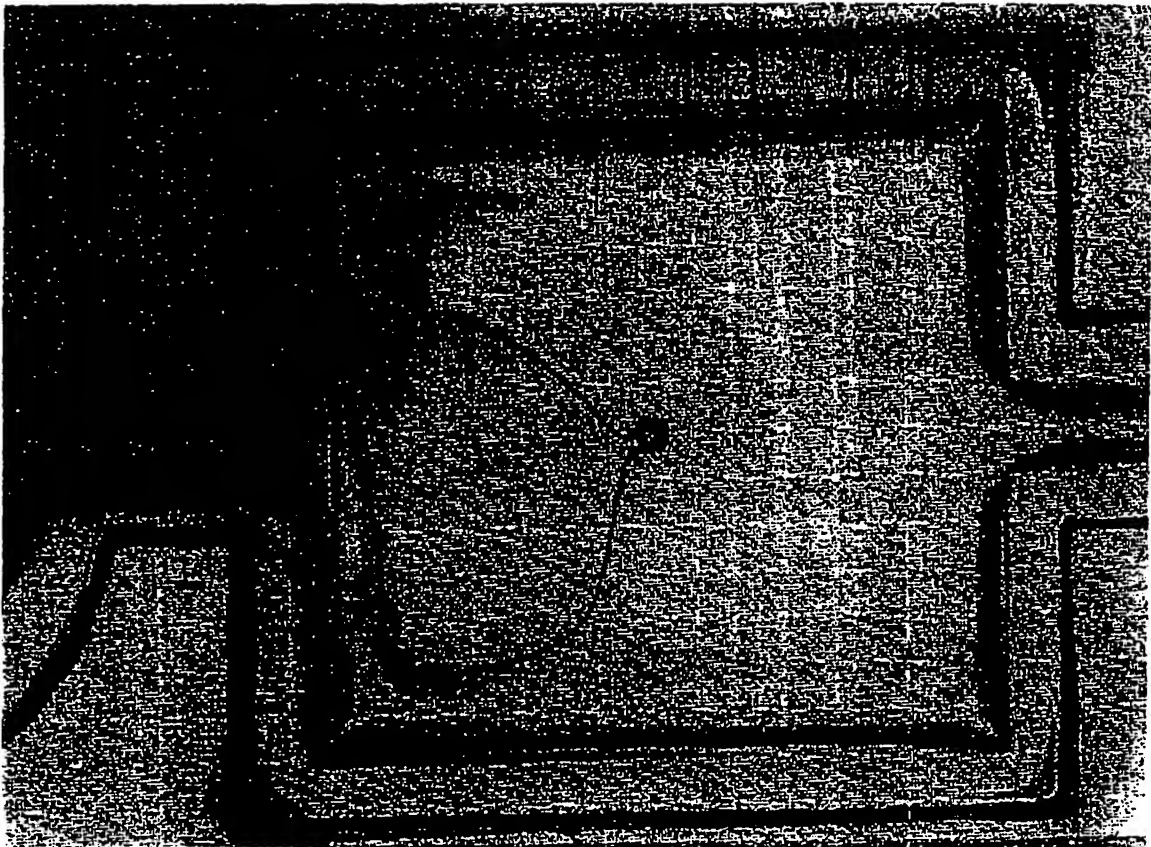


FIGURE 11



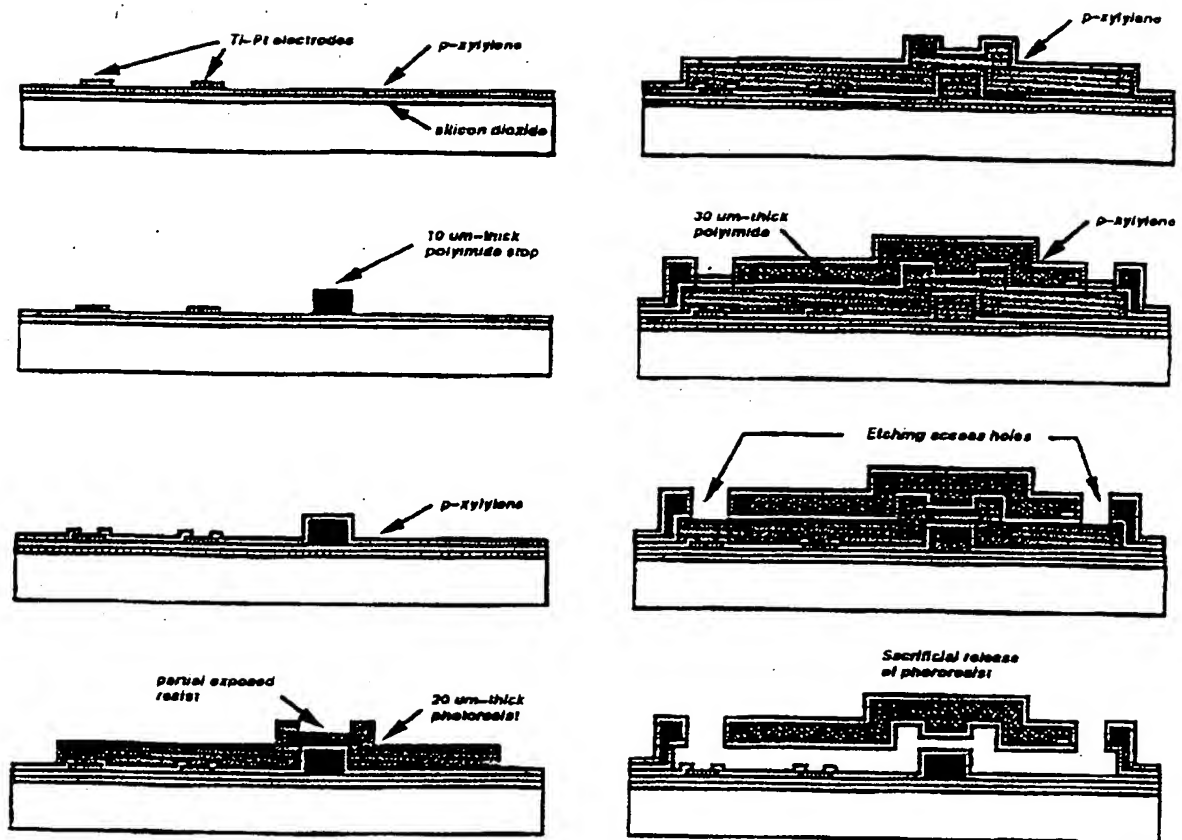
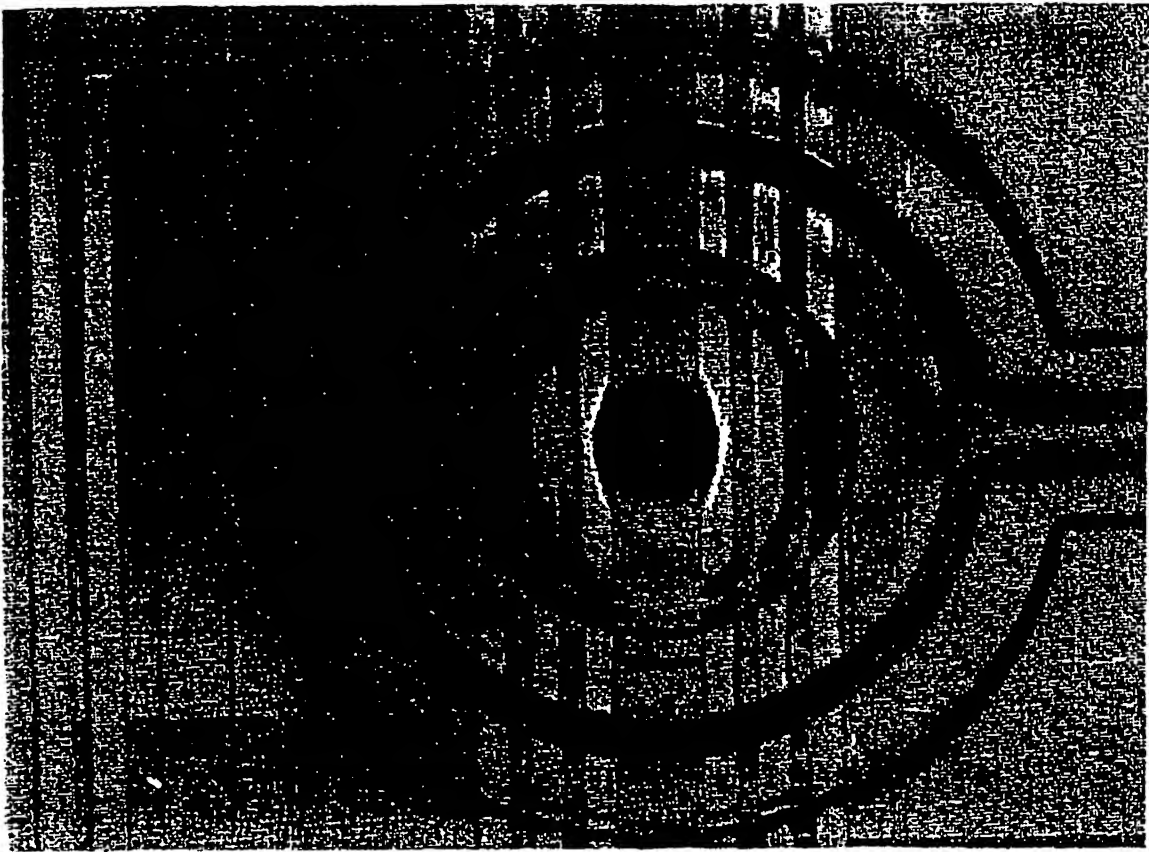


Fig. 13: Process flow of bubble pump and capillary valve

FIGURE 12



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14054

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : G03F 7/00

US CL : 430/311, 313, 314, 319, 394

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 430/311, 313, 314, 319, 394

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------------|-----------------------|
| Y | US 4,153,855 A (FEINGOLD) 08 May 1979, column 2, lines 6-37 and claim 2. | 1-24 |
| Y | US 5,265,327 A (FARIS ET AL) 30 November 1993, abstract, column 10, line 53 to column 11, line 12 and claims 3 and 4. | 1-24 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *B* earlier document published on or after the international filing date | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *A* document member of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

21 NOVEMBER 1997

Date of mailing of the international search report

23 DEC 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

KATHLEEN DUDA *Kathleen Duda*
Telephone No. (703) 308-0661

Page Blank (usps)